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CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/021,955	LUPSKI ET AL.	
	Examin r	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-7,35-40 and 42-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,35-40 and 42-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/26/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on August 25, 2004 has been entered.

2. The Declaration under 37 CFR 1.132, submitted on August 25, 2004 is entered.

3. Claims 4, and 40 are amended, claims 8-34, 41 are canceled. New claims 51-61 are added. Claims 1-7, 35-40, 42-61 are currently pending in this application.

New Grounds of Rejections necessitated by Amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 35-40 and 42-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance

Presence and Absence of Working Examples

Nature of Invention

Level of Predictability and unpredictability in the art

Nature of the Invention :

Claims 1-7 are drawn to a method of diagnosing myelinopathy in an individual and claims 35-40, and 42 are drawn to a method of detecting the presence or absence of any mutation in a periaxin polynucleotide and its association with any myelinopathy. Further, Claim 7 is drawn to a specific alteration in a periaxin polynucleotide and Claim 36 is drawn to an association between a specific mutation in periaxin and any myelinopathy. Claims 4 and 40 are broadly drawn to a broad range of diseases of myelinopathy such as Charcot-Marie-Tooth (CMT) syndrome, hereditary neuropathy with liability to pressure palsies (HNPP), Dejerine-Sottas syndrome (DSS), congenital hypomyelinating neuropathy (CHN), and Roussy-Levy syndrome (RLS). Claim 50 is drawn to a DSS. Claim 58 drawn to a prominent sensory neuropathy. Claims 53-56 are drawn to a method of identifying alteration comprising homozygous, heterozygous and compound heterozygous periaxin mutations. Claims 57 and 61 are drawn to a method of identifying an individual suspected of having myelinopathy or being a carrier of myelinopathy.

Amount of Direction and Guidance:

The specification discloses the identity of several mutations in periaxin polynucleotide and their locations (see Figs. 4 and 9). The specification on page 14, asserts a correlation between the human orthologue of murine and rat periaxin (Prx) with human inherited myelinopathy and further asserts that human periaxin gene which encodes two PDZ domain proteins, is required for the maintenance of peripheral nerve myelin. The specification teaches that based on knockout animal models, periaxin is correlated to the proper formation of myelin sheaths and the

specification broadly discloses the identification of recessive Prx mutations comprising nonsense and frame shift mutations in the periaxin gene. The specification asserts that based on the common known methods in the art, mutations in other periaxin polynucleotide sequences (for example SEQ ID No. 76) could be detected. The specification discloses mutations in SEQ ID No.1 and extrapolates the use of similar techniques to detect mutations in other periaxin polynucleotides (for example SEQ ID NO.76). The specification discloses mutations in other genes associated with some myelinopathy (see page 20) (such as DNA rearrangements in CMT patients caused by mutations in MPZ, Cx32, EGR2, and mutations in MPZ and EGR2 in DSS patients). Further the specification on page 21, asserts the function of periaxin in the maintenance of the myelin sheath based on animal studies. However, the specification has not established that a statistically significant association exists between all of the specific mutations disclosed in the specification, and any myelinopathy, or any specific myelinopathy, or that a predictable correlation can be made as to an association between any mutation in the periaxin gene and any myelinopathy or any specific myelinopathy. Further the specification has not established that any periaxin mutation is associated with DSN and no predicatble correlation is established that any homozygous periaxin mutation or that two different mutations in a compound heterozygote are associated with myelinopathy in general. With regard to the new claims 51-61, the specification (on page 65, example 3) provides evidence for compound heterozygous with a deletion and a transition mutation associated with specific types of myelinopathies that is one form of CMT and DSN. However, the specification fails to establish that any alteration in Prx is diagnostic for myelinopathy in general, nor that the presence of a single mutation in a single allele would indicate that someone is susceptible to myelinopathy or a carrier of a periaxin associated

myelinopathy as it is clear that mutations in Prx exist which are not only not diagnostic but also not associated with myelinopathy (table 2). The specification exemplifies that the presence of an alteration in the periaxin gene is not necessarily diagnostic for myelinopathies or an indicator that someone is a carrier for a disease causing mutation, as broadly claimed.

Presence and Absence of working examples:

The specification discloses a method of screening Prx mutations in some family studies and detected mutations comprising a deletion and a transition in the affected patients with peripheral neuropathy. The specification correlates the mutations with the loss of function of Prx gene in relation to studies in rat (example 4). The examples 2-4 in the specification establish a positive correlation between the presence of a periaxin polynucleotide comprising mutation which results in a truncated periaxin polypeptide in patients with undisclosed myelinopathy, wherein said patients have two aberrant forms of periaxin polypeptides. Although the specification does not demonstrate any alteration in Prx is associated with myelinopathies in general, the specification asserts that the mutations could be associated with loss of function of the periaxin polypeptide. It is noted, however, that these examples also establish that the mere presence of a mutation (i.e., only a single copy) is NOT associated with the disease as in HOU579 family, wherein the unaffected parents had an allele with single mutated Prx polynucleotide and another allele of wild type Prx polynucleotide. Further there is no description of the type of peripheral neuropathy of the affected patients. (see page 65, example 3). Further examples in the specification merely asserts correlation between mutations in Prx with myelinopathy in general, however no specific mutation is associated with any of the different types of myelinopathies as exemplified by the example 8 in the specification (see page 72). Further table- 2 shows that the unaffected control

subjects contain mutations in periaxin. The specification does not teach whether the mutations in table-2 are associated with loss of function or if they are statistically associated with any specific peripheral neuropathy or any specific myelinopathy. Thus the mere detection of an alteration in Prx gene is not diagnostic for myelinopathies in general. The specification fails to show that all alterations are diagnostic or associated with myelinopathies because the specification shows that carriers having an alteration are unaffected with myelinopathy (table-2). Thus all carriers having an alteration or mutation in Prx would not be carriers of disease-causing Prx mutations. The specification does not provide guidance as to which Prx alterations are predictably associated with myelinopathy in general, or not associated with myelinopathy. Further the specification does not provide guidance as to which Prx alterations would indicate an individual being a carrier of disease-causing mutations or not.

Level of Predictability and unpredictability in the art :

Predictability in the art suggests mutations in genes other than the specific periaxin gene, are associated with specific type of myelinopathy, for example Boss et al. (USPN. 5,691,144) teaches mutations in connexin-32 are associated with X-linked Charcot-Marie-Tooth (CMT) disease, Timmermann et al. (Neurology, Vol. 52, pp. 1827-1832, 1999) teach a missense mutation in EGR2 gene in association with Dejerine-Scottas syndrome (DSS). Lupski et al. (USPN. 5,780,223) teach DNA duplication in CMT1A gene sequence association with autosomal dominant CMT disease, and Roa et al. (Nature Genetics, Vol. 5, pp. 269273, 1993) teach that some point mutations in peripheral myelin protein 22 (PMP22) gene are associated with CMT1A, while others are associated with DSS (Fig.3, page 271). With regards to the specific periaxin gene Guilbot et al. (Human Molecular Genetics, Vol. 10, No.4, 2001), teach

periaxin is responsible for CMT4F, an autosomal recessive form of CMT disease, and Gillepsie et al. (Neuron, Vol. 12, pp. 497-508, 1994) teach role of periaxin in rat peripheral nervous system and discloses that periaxin localization in schwann cells and its possible role in ensheathment. Further, Takashima et al. disclose periaxin mutations cause a broad spectrum of demyelinating neuropathies and disclose that affected patients with CMT or DSN comprise Prx mutations in homozygous condition, that is both alleles are mutated with a specific mutation and the unaffected family members are carriers for myelinopathy, that is a single allele of Prx is mutated (Takashima et al. Ann. Neurol., Vol. 51, pp. 709-715, 2002). Kijima et al. disclose yet another Prx mutation causing early-onset but slow-progressive CMT disease (Kijima et al. J Hum Genet., Vol. 49, pp. 376-379, 2004). However, the art does not establish a predictable association that any specific mutation in periaxin or any other genes is predictably associated with all of the large number of diseases encompassed by the recitation of "myelinopathy". For example Roa et al. teach that while some point mutations in PMP22 are associated with CMT1A, others are associated with DSS. Further, while Boerkoel et al. (Am. J. Hum. Genet., Vol. 68, pages 325-333, 2001) teach that certain specific mutations are associated with DSN, when both copies of periaxin gene are altered, Boerkoel et al. further teach that the family members with only one altered copy of periaxin gene were not affected and also teach a number of missense mutations in normal and unaffected family members. Further, Takashima et al. teach similar study, wherein DSN or CMT affected patients have two mutated alleles where as the unaffected have one mutated allele with no demyelination. The art is further silent with regard to a predictable association between any specific alteration or mutation in periaxin and a representative number of diseases encompassed by the term "myelinopathy". Diseases

encompassed by the term "myelinopathy" include a large number of heterogeneous diseases with differing symptoms and associations to genetic mutations. To date, however, there is no evidence that the association of an alteration or mutation in a specific gene and a specific form of myelinopathy can predictably correlate the presence of any other, or all, specific myelinopathy encompassed by the broad term "myelinopathy". The claims further broadly encompass detecting an association between any specific mutation in periaxin, and an association to a specific unnamed myelinopathy. The specification, however does not establish a statistically significant association with any of the disclosed mutations in periaxin, and any specific form of myelinopathy such that the skilled artisan might be able to predictably correlate which mutations in periaxin would be associated with a specific form of myelinopathy. The mere detection of an alteration in Prx gene is not associated with myelinopathies in general. Further, to date, no teaching is available in the art with regards to a universal correlation between any mutation in periaxin and an association with any general or specific type of myelinopathy. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with any particular type of myelinopathy. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of any particular mutation in periaxin with any particular type of myelinopathy. Further, CMT is inherited in three forms, i.e., autosomal dominant, autosomal recessive and X-linked conditions. The specification fails to support an association of a mutation in periaxin with all the three forms of CMT.

In addition, the specification does not establish the identity of any specific critical nucleotide or amino acid alteration(s) that are associated with loss of function or are associated with

myelinopathy. The missense mutations in table-2 were also found in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or compound heterozygous for other mutations in periaxin. It is clear from the teachings in table-2, that the mere presence of an alteration in periaxin such as a substitution or deletion is not indicative of myelinopathy. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear whether these mutations or any specific mutation will have a significant affect or not. With regard to the heterozygous carriers carrying a Prx mutant allele, the specification fails to establish that the mere presence of an alteration in Prx as claimed broadly in the new claims 51-61 would result in carriers of disease causing Prx mutant alleles, or result in susceptibility to any myelinopathy.

Quantity of Experimentation Necessary:

Given the lack of guidance in the specification and the unpredictability in the art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that any mutation in periaxin is significantly associated with any specific myelinopathy. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of myelinopathy, such as CMT, DSS, and matched controls to determine if any general alteration or mutation in periaxin or any specific claimed alteration or mutation in peraxin, was associated with any myelinopathy in general. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the

art. Further, it would require a large amount of experimentation to distinguish which Prx mutant allele carriers are associated with the myelinopathy in general or which Prx mutant allele carriers are not associated with myelinopathy. Thus a mere presence of an alteration is not diagnostic for any myelinopathy or is not diagnostic for identifying a carrier having a disease-causing Prx mutant allele. Therefore, given the lack of guidance from the specification as to any statistical association between the claimed association of any mutation in peraxin polynucleotide and any myelinopathy, and the unpredictability taught in the art as to some point mutations in other genes such as PMP22 are associated with one form of CMT, while other mutations in the same PMP22 are associated with DSS, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed.

Response to arguments

5. Applicants' arguments and amendment have been fully considered and found persuasive in part.

6. With regard to arguments on the election of the SEQ ID Nos. Applicants' arguments are fully considered and is found not persuasive because of the following reasons: these sequences comprise patentably distinct SNPs or mutations of the periaxin gene. These SNPs or mutations result in patentably distinct periaxin sequences with different structures. These variant polynucleotides are structurally and functionally different. Hence the restriction requirement is still deemed proper and the finality is maintained.

7. With regard to the rejection made in the previous office action under 35 USC 112, second paragraph, Applicants' amendment is fully considered and the rejection is withdrawn herein.

8. With regard to the rejection made in the previous office action made under 35 USC 102(a), Applicants' arguments and the declaration under 37 CFR 1.132 are fully considered and the rejection is withdrawn in view of the declaration.

9. With regard to the rejection made in the previous office action made under 35 USC 103(a), Applicants' arguments and amendment are full considered is considered and the rejection is withdrawn in view of the persuasive arguments.

10. With regard to the rejection under 35 U.S.C. 112, first paragraph, Applicants' arguments are fully considered and found not persuasive.

On page 9 (paragraphs 2 and 3) of the Applicants' response, Applicants argue that the pending claims are enabled, as the disclosure teaches a variety of mutations associated with myelinopathies, such as DSN and argue that the Applicants are not claiming periaxin for a wide range of diseases, but those as part of phenotypically narrow range of myelinopathies. Applicants' arguments are fully considered and are found not persuasive. The instant claims broadly recite diagnosing myelinopathy, which comprises a wide range of myelinopathies and are not limited to the asserted "phenotypically narrow range of myelinopathies". Further "phenotypically narrow range of myelinopathies" is not defined. Thus it is not clear what diseases belong to this "phenotypically narrow" range of myelinopathies nor which mutations would be predictably diagnostic or associated with this "phenotypically narrow" range. The instant claims require the skilled artisan to assay each possible Prx mutation, to determine which are associated in this undefined "phenotypically narrow range". This leads to further experimentation to determine which mutations are associated with this undefined

"phenotypically narrow" range and to further define the scope of applicant's asserted "phenotypically narrow range of myelinopathies".

All the claims require is that diagnosis results from the detection of an alteration in Prx, but the specification does not provide a predictable correlation that the mere presence of an alteration in Prx would predict an association with myelinopathy in general, be diagnostic of myelinopathy in general, or any specific myelinopathy. In fact, the specification provides evidence that the mere presence of a mutation (i.e., only a single copy) is NOT diagnostic of disease as in HOU579 family, wherein the unaffected parents (hyterozygous carriers) had an allele with single mutated Prx polynucleotide and another allele of wild type Prx polynucleotide (see page 65, example 3). In table 2, the specification further provides evidence that the mere presence of an alteration in Prx is neither diagnostic for nor associated with myelinopathy in general nor any specific myelinopathies. These mutations neither predict an increased susceptibility, nor would indicate someone as being a carrier of a Prx associated myelinopathy.

On page 9 (paragraph 3) of the Applicants' response, Applicants also argue that the claims are not drawn to any myelinopathy, but are drawn to those myelinopathies associated with an alteration in periaxian. However the specification has not provided any predictable way for the skilled artisan to determine which mutations are associated or which types of myelinopathies would be "myelinopathy" resulting from an alteration in periaxin. To practice the invention as broadly as it is claimed, the skilled artisan would be required to actually assess each and every variant to detect if it was diagnostic for myelinopathy in general or any specific myelinopathy, or if it would indicate increased susceptibility for myelinopathy or indicate someone as a carrier of a Prx associated myelinopathy.

On page 9 (paragraph 4) of the Applicants' response, Applicants also argue that the published literature since the filling of the application and the original disclosure provide evidence that alterations in Prx are indicative of nyelinopathies and provide how to make and use of the invention. Applicants' arguments are fully considered and found not persuasive. Examiner reviewed the published papers provided by the applicants and noted that neither the published papers nor the instant disclosure provide a predictable correlation that all alterations in Prx gene results in myelinopathies in general, any specific myelinopathy or which Prx mutations are periaxin associated myelinopathy mutations. As discussed in the above rejection, Kijima et al. disclose a Prx mutation causing early-onset but slow-progressive X-linked CMT disease , wherein one patient was a female (XX) carries two copies of Prx mutation and other two patients are males (XY) carries a single copy of Prx mutation on X chromosome, thus as expected for X-linked diseases (Kijima et al. J Hum Genet., Vol. 49, pp. 376-379, 2004). And Takashima et al. teach another study, wherein DSN or CMT affected patients have two mutated alleles where as the unaffected have one mutated allele with no demyelination. The art is silent with regard to a predictable association between any specific alteration or mutation in periaxin and myelinopathy in general. The art does not establish a predictable association that any specific alteration in periaxin is predictably associated with all of the large number of diseases encompassed by the recitation of "myelinopathy".

On page 10 (paragraph 1) of the Applicants' response, Applicants' argue that it is not required to provide statistically significant data for enablement of claims. And the scope of the enablement must bear a reasonable correlation. And asserts that a reasonable correlation was indeed provided in the specification, and asserts that Prx shown with DSN and the highly related

myelinopathies are within the scope of reasonable correlation. These arguments are fully considered and found not persuasive because the mere identification of an alteration does not provide a reasonable correlation with myelinopathies in general. As discussed above the unaffected individuals with one copy of the Prx alteration are not afflicted with any myelinopathy and thus the specification fails to establish any reasonable correlation with myelinopathies, specifically or in general, or that the mere fact that an alteration in Prx exists is diagnostic. Further, while some mutations indicate an individual as being a carrier of Prx associated myelinopathy mutation, the specification has provided no guidance as to how one of skill in the art would be able to predict which mutations, from the extremely large number of possible Prx alterations that are known to, exist or that are yet to be detected, would be indicative of diagnostic, susceptibility, or carrier status. As such, the claims are not commensurate in scope with the guidance in the specification or the art.

On pages 10 –11 (paragraph 2-3 of page 10 and lines 1-2 of page 11) of the Applicants' response, Applicants further argue that claims are commensurate with the teachings in the specification and the Prx mutations are associated with myelinopathy in general or any of the specific myelinopathies. Applicants further argue that Examiner misconstrues the paragraph 0244 of the instant specification and explains that individuals can be carriers for the disease by being heterozygous for the mutation. This argument has been thoroughly reviewed. The cited paragraph indicates carriers are not affected even though they carry an alteration in Prx. However claim 1 is broadly drawn to the detection of an alteration in a periaxin, being diagnostic of myelinopathy in general. The examiner agrees that the specification provides that certain specific mutations, while not diagnostic, do indicate an individual as being a carrier of a specific

disease associated mutation. However the claims are also broadly drawn to detecting susceptibility to any myelinopathy or being a carrier of a Prx associated myelinopathy. The specification has demonstrated that all Prx mutations are not diagnostic, or indicative of a carrier for any specific myelinopathy or myelinopathy in general. Further, the specification does not teach how one skill in the art could predictably determine which mutations were diagnostic, or indicative that a subject was a carrier of Prx associated myelinopathy. Further, the specification has not taught which mutations would be predictably associated with a specific myelinopathy. While myelinopathies possess some phenotypic similarities, they also possess differences. However, the specification has not provided guidance as to how or why one mutation is associated with CMT, while another is diagnostic for DSN. To practice the invention as broadly claimed, the skilled artisan would have to carry out studies on each possible mutation to determine if it was or was not diagnostic, indicative of a carrier, susceptibility etc. Such experimentation is related with trail and error analysis with no predictability of out come until effective reduction to practice.

On page 11-12 of the Applicants' response, Applicants' argue that the declaration filed on December 18, 2003 discusses the issues and concerns raised by the Examiner regarding the data in table-2 of the specification and request the examiner to reconsider the declaration. Applicants' arguments have been fully considered. The declaration filed on December, 18, 2003 has been reconsidered in light of the response's traversal regarding table 2, however neither the arguments in the response nor the declaration were persuasive. The declaration indicates that the instant specification discloses several mutations in Prx cause a broad spectrum of demyelinating neuropathies, that include CMT1 and DSN as show in specific paragraphs (0244 and 0260) of

the specification. The declaration also discloses that the specification teaches (at least in examples 2-8 as cited in paragraphs 0062, 0242, 0244, 0246, 0247, 0260, 0261, 0268 and 0273) a skilled artisan to recognize and assess a difference in a polymorphism and a disease-causing mutation. With regard to the data in table 2, examiner notes that table-2 shows Prx mutations in unaffected controls. The specification does not teach if patients had one copy of mutation, or if they were homozygous or compound heterozygous for other mutations in periaxin. It is clear from the teachings in table-2, that the mere presence of an alteration in periaxin such as a substitution or deletion is not diagnostic for myelinopathy. Further, with regard to the 2145T-> A and 274Δ C mutation in claim 36, and the R196X, C715X, or R82FSX96, the specification has provided no data as to whether these mutations are even associated with myelinopathy. Since the specification has not identified any specific critical amino acid alteration, it is further unclear whether these mutations or any specific mutation will have a significant affect or not. With regard to the heterozygous carriers carrying a Prx mutant allele, the specification fails to establish that the mere presence of an alteration in Prx as claimed broadly in the new claims 51-61 would result in carriers of disease causing Prx mutant alleles. Applicants' arguments with regard to the differences in a polymorphism vs a disease-causing mutations are fully considered. However, based on these arguments it is clear that each and every mutation or alteration in Prx would not be a disease-causing mutation. Thus it further clarifies that the mere detection of an alteration is not diagnostic yet the claims broadly encompass such mutations or alterations. The declaration asserts at page 3, that one of skill in the art would know how to discern between a polymorphism and a disease causing mutation, because if an alteration is a polymorphism it is not identified controls and /or does not segregate with the disease phenotype. This argument has

been thoroughly reviewed but was found unpersuasive. Such assertions highlight the need that the skilled artisan would require experimentation to determine whether an alteration was diagnostic or associated with myelinopathies – either prominent sensory neuropathies or to specific meylinopathies. However, the claims are not drawn to determining whether an alteration is diagnostic or disease associated, but to methods of diagnosing or determining increased susceptibility or a carrier status merely based on detection of an alteration. However, as exemplified by the specification all alterations in Prx are not predictably correlated with myelinopathies, including prominent sensory neuropathies.

On page 12 of the Applicants' response, Applicants' arguments regarding SEQ ID No. 76 have been fully considered. Applicants' argue that SEQ ID NO. 76 is a variant of SEQ ID No. 1, which is specifically exemplified in example 8, and argues that it is unclear why this specific SEQ ID was at issue. Examiner discussed this specific SEQ ID No. 76, because Applicants' elected this SEQ ID, however it was not clear if the variant SEQ ID 76 was associated with myelinopathies. The issue was raised because some of the claims are specifically drawn to SEQ ID No.76. With regard to arguments regarding the claims 49 and 50, it is noted that the 112/ first paragraph requires that the specification enable how to make and "use" the claimed invention. As already discussed, the specification exemplifies that any alteration in periaxin is not predictably associated with myelinopathy, nor does the specification teach how to determine, other than by actually performing assays requiring a large amount of inventive effort, which alterations are or are not associated with myelinopathy. Therefore, the specification has not enabled the skilled artisan to use the invention as broadly as it is claimed.

On page 13 of the Applicants' response, Applicants argue that undue experimentation is not required, and a considerable amount of experimentation is permissible, if it is mere routine or if the specification provides a reasonable amount of guidance and direction and further that actual reduction to practice is not required. Applicants' arguments are fully considered, but were found not persuasive. In the instant case, the specification does not provide a reasonable amount of guidance and direction in which the experimentation should proceed because the specification does not teach which mutations in Prx would predictably be diagnostic or have any effect on the activity or function of periaxin. The specification fails to establish any general diagnsotic correlation with myelinopathies in general or prominent sensory neuropathy. To practice the invention as broadly as it is claimed the skilled artisan would be required to actually assess each and every variant to detect if it was diagnostic for myelinopathy in general or any specific myelinopathy. Because the specification provides no guidance as to which mutations are diagnostic or associated with myelinopathies, or have any effect on the function of periaxin, such experimentation would be replete with trial and error analysis with no ability to predict outcome. Such experimentation is not routine, but requires inventive effort to actually determine which mutations fall within the scope of the claimed invention. In the instant case, the specification does not provide any guidance or direction as to which mutations would have a significant effect or not nor does it provide guidance as to which direction the experimentation should proceed, other than to actually asses each alteration. Without such experimentation, there is no way to actually predict which mutations would fall within the scope of the claimed invention. Such experimentation is considered undue.

On page 14 of the Applicants' response, Applicants argue that a considerable number and content of working example are provided in the specification, that commensurate with the scope of the claims and further argue that identification of exemplary mutations associated within the spectrum of myelinopathies is more than sufficient to show that the claimed invention is enabled. Applicants' arguments are fully considered and found not persuasive. The working examples as cited in paragraphs 0235-0241, provide support only to those mutations or alterations that are associated with a particular type of myelinopathy. It should be noted that these working examples do not provide evidence that a mere presence of an alteration is diagnostic for myelinopathies in general or prominent sensory myelinopathies as claimed. Further example 8, in paragraph 0268 discloses the results of two families in a pedigree with patients affected either with DSN or with one form of CMT. As discussed above the heterozygous carriers are not affected and thus as it is broadly claimed, not each and every alteration or mutation in Prx is not diagnostic of myelinopathies in general. Further as exemplified by the specification, the presence of an alteration does not necessarily indicate one to be susceptible or to be a carrier for a Prx associated myelinopathy. With regard to the assertions made on page 14, with regard to examples 1-3, such arguments are directed to how to find embodiments which fall within the scope of the broadly claimed invention. Such teaching in the specification do not teach which alterations would be predictably associated with disease, but teach and invite one to determine which embodiments fall within the scope of the invention. Such does not provide a teaching of how to make, but how to "find", which is not the standard for enablement. Example 8 shows some mutations are associated and under certain conditions are diagnostic of disease, however, it does not teach what other mutations would also be

predictably associated. The examiner is not requiring that the specification actually test all of the possible alterations in Prx, but that the specification should provide guidance as to which alterations would be predictably associated. This does not require that the specification should screen each and every possible alteration. But, for example- to highlight the examiner's point, the response addresses "putative loss of function mutations", however the specification provides no guidance as to which mutations in Prx would likely result in loss of function. Other than the specific diagnostic alterations taught in the specification, given that lack of guidance in the specification, the skilled artisan would be unable to predictably determine what other alterations would result in loss of function. Thus the specification fails to established any reasonable correlation that any alteration in Prx is associated with myelinopathies in general.

On Page 15 of the response, Applicants' argue that under 112, it is not a requirement to describe exactly the subject matter claimed and assert that it is not necessary that a patent applicant test all the embodiments of his invention. Applicants' assertions are fully considered, however, the arguments are not persuasive because the examiner has not rejected the claims based on lack of description nor has the examiner required applicant to test all embodiments. Applicants' further argue that the specification provides the identification of exemplary mutations associated within the spectrum of meylinopathies and it more than sufficiently enables the scope for myelinopathies. Applicants' arguments are fully considered and found unpersuasive because the specification shows that in fact different mutations are associated with a specific myelinopathy, but provide no guidance as to why such mutations are not associated or diagnostic of other types of myelinopathies. Applicants further argue that it is a routine for a skilled artisan to determine whether or not a particular sequence variation is associated with a

disease state and remind the examiner that the claims are directed to only those myelinopathies resulting from a periaxian alteration. Applicants assertion are fully considered and found unpersuasive because the claims are not directed to detecting whether or not a sequence variation is associated with disease state, but to diagnose, to identify individuals with increase susceptibility and carrier status. Further it is noted that the specification does not provide guidance to determine which alterations in Prx are predictably associated with or diagnostic of myelinopathies in general, prominent sensory neuropathy or specific myelinopathy and which alterations in Prx are not. Experimentation to determine which alteration in Prx would fall within the scope of the claimed invention is replete with unpredictable trial and error analysis-which is undue.

On page 16 (paragraphs 1-2) of the response, Applicants assert that the specification has provided both sufficient numbers of PRX mutations and associating myelinopathies, and provided some experimentation, showing correlation between particular mutations and disease status and amount of direction needed to enable the invention. Applicants also assert that the specification have provided more than sufficient number and content of working examples to support the association of Prx mutations with a range of myelinopathies within the CMT1 category which is further supplemented by the examples in the art and the specification at paragraphs 0062-0064, 0268 showing association of multiple mutations in Prx with the spectrum of PRX-associated peripheral neuropathies that provide a variety of means to determine periaxin sequence variations. Applicants' arguments are fully considered and found not persuasive because such arguments are directed to how to find embodiments which fall within the scope of the broadly claimed invention. Such teaching in the specification do not teach which alterations

would be predictably associated with disease, but teach and invite one to determine which embodiments fall within the scope of the invention. Such does not provide a teaching of how to make, but how to "find", which is not the standard for enablement. The art and working examples as cited in paragraphs 0062-0064, 0268, provide support only to those mutations or alterations that are associated with a particular type of myelinopathy. It should be noted that these working examples do not provide evidence that a mere presence of an alteration is diagnostic for myelinopathies in general or prominent sensory myelinopathies as claimed. The specification fails to establish any general diagnostic correlation with myelinopathies in general or prominent sensory neuropathy. To practice the invention as broadly as it is claimed the skilled artisan would be required to actually assess each and every variant to detect if it was diagnostic for myelinopathy in general or any specific myelinopathy. Because the specification provides no guidance as to which mutations are diagnostic or associated with myelinopathies, or have any effect on the function of periaxin, such experimentation would be replete with trial and error analysis with no ability to predict outcome. Such experimentation is not routine, but requires inventive effort to actually determine which mutations fall within the scope of the claimed invention. In the instant case, the specification does not provide any guidance or direction as to which mutations would have a significant effect or not nor does it provide guidance as to which direction the experimentation should proceed, other than to actually asses each alteration. Without such experimentation, there is no way to actually predict which mutations would fall within the scope of the claimed invention. Such experimentation is considered undue.

With regard to the Applicants' assertions on page 16 (paragraph 3) and page 17, regarding the evidence provided in the specification for a group of highly related diseases having

significant phenotypic overlap likely to associate with Prx defects, Applicants' arguments have been fully considered, however the specification shows that diagnosis is unpredictable with regard to each mutation. For instance, in example 3, a compound heterozygous for deletion mutation 2787 C and 2857C>T is only associated with CMT1 and is not associated with DSN, whereas a compound heterozygous for deletion mutation 2289 T and 1102 C>T mutation is associated with DSN and not associated with CMT1. While the myelinopathies set fourth in the specification have phenotypic similarities, they also have differences, which is highlighted by the fact that the mutations in the specification are not generally associated with the groupings of myelinopathies set forth in the Applicants' response. Thus by the mere detection of a mutation, the skilled artisan would not be able to predict which mutations are disease susceptible or which mutations are disease causing or indicate an individual as a carrier for myelinopathy. Therefore the rejection is maintained.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
January 4, 2005

Jehanne Sitton
JEHANNE SITTON
PRIMARY EXAMINER
1/6/05